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Tropical Disease – A Challenge for Epidemiology

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Ross's *a priori* Pathometry – a Perspective

Probably the most important contribution made by tropical medicine to the theoretical and methodological corpus of contemporary epidemiology is the classic work of Sir Ronald Ross, published between the years 1904 and 1917, and called by its author, variously: 'a theory of happenings' (Ross 1911*a*); '*a priori* pathometry' (Ross 1915, 1916); or 'constructive epidemiology' (Ross 1929).

So bold a praise of this particular work may be met with a certain scepticism. Ross is better known to the medical community as the discoverer of the mosquito transmission of malaria than as the author of a far-reaching theoretical approach to the study of disease in populations. Though many epidemiologists have heard of Ross's work, very few contemporary workers are familiar with it in any detail. Indeed, familiarity is to be gained only by reading the original papers, as Ross's work is rarely cited today, and has not been reviewed in recent years (with the exception of a discussion by Serfling in 1952). It is time to remind ourselves of the historical importance, the charm and the power of this theoretical epidemiology of Sir Ronald Ross.

This review will concentrate on four general points: (1) the background to Ross's theoretical work; (2) its content; (3) its claim to originality; and (4) its relevance to epidemiological work today.

Historical Background

Ronald Ross was one of those men of extraordinary talent and self-discipline to emerge during the Victorian era. Born in 1857 at Almora in Northern India, he was educated in England, studying medicine at St Bartholomew's Hospital in London. After becoming a licentiate in the Society of Apothecaries in 1881, he returned to the orient as an officer in the Indian Medical Service. There he spent the following eighteen years, except for periods in 1888–89, and again in 1894–95, when he returned to England. On the second of these visits he met Patrick Manson, founder of what is now the London School of Hygiene and Tropical Medicine, who encouraged Ross to apply himself to the problem of the transmission of malaria. Ross returned to India in 1895, full of enthusiasm for this project, and after three years of concentrated effort was able to telegraph to Patrick Manson that he had traced the life cycle of a malaria parasite through a mosquito. This was certainly medical adventure and success on the grandest scale – and led to Ross's election to the Royal Society, and to his receipt of the second Nobel prize in medicine, awarded in 1902 (Megroz 1931, Ross 1923).

On the other hand, this well-known story does not do full justice to the complexity of Ronald Ross the man. Ross was not only a man who examined mosquitoes – he also wrote and published novels, poetry and plays, and composed music. If such were the pursuits of many cultured men in that more leisurely era, Ross had a yet more remarkable trait: a passion for mathematics. Nurtured ever since his school days, and a constant theme throughout his life, this interest in mathematics was not just for pleasure; it was in earnest. Soon after his return to Britain after his successes in India, Ross published his first of several papers in pure mathematics, entitled 'The Algebra of Space' (Ross 1901).

During the early years of this century, Ross waged a constant and often acrimonious battle for the acceptance of what he called (in what was perhaps a subtle manifestation of his mathematical turn of mind) his 'mosquito theorem' (Ross 1908, &c.). The implication of this theorem, that mere reduction of mosquito populations in the field provided a means of preventing malaria transmission, was clear to Ross, but not immediately so to his contemporaries in the medical and public health professions. The resistance to this inference may be difficult for us to understand today. It was a classic example of the difficulty which plagues persons of a qualitative and descriptive outlook, when confronted with what is essentially a quantitative problem. The argument against Ross's idea took the following form: it is impossible to totally eradicate the mosquitoes in an area (Ross admitted this) . . . thus there will always be some mosquitoes remaining (Ross admitted this) . . . thus malaria transmission will continue, and mosquito control is a waste of time and effort (here Ross disagreed) (Ross 1904*a*, *b*). The fallacy in such an argument is clear to one who is used to thinking in terms of numbers, of probabilities, of life spans and population densities. But its fallacy may not be immediately clear to one whose parasitology consists merely of the memorization of life cycles. Its refutation requires a quantitative argument. Perhaps it may be counted among the happy ironies of history that no one was in a better position to construct such an argument than was Ronald Ross, at once mathematician, and physician, and epidemiologist. It was the challenge of convincing the world that mosquito control was a practical public health undertaking that stimulated Ronald Ross to develop what came to be called the *a priori* pathometry.

Ross's first attempt at a quantitative argument on this issue of mosquito control was in a paper entitled 'On the logical basis of the sanitary policy of mosquito reduction', read at an International Congress of Arts and Sciences, in St Louis, Missouri in 1904. In this paper he developed what he called a 'centripetal law of random wandering', which described how the control of mosquitoes in one area affects the absolute size of the population in neighbouring areas, as the mobility of individual mosquitoes allows the population to diffuse into control areas.

The main importance of this 1904 paper is in its position as Ross's first published attempt at tackling an epidemiological problem in mathematical terms. In it he dealt with only a segment of the malaria problem, however, as he did not discuss the relationship of the mosquito population size to malaria transmission.

The crucial synthesizing step was taken in 1908, within a lengthy report prepared by Ross on the status of malaria control on the island of Mauritius. In this document, we find the first clear formulation of Ross's great contribution to epidemiological methodology. Here the term 'pathometry' first appeared, a word later defined as 'the quantitative study of disease' (Ross 1928). In the general discussion section of this report Ross attempted to specify, and to tie together, all the major factors responsible for the transmission and the maintenance of malaria in a human population. He did this using the medium of a simple algebraic equation, structured so as to define the *number* of *new* infections of malaria which should occur within one month. The equation is as follows:

$$\text{No. of new infections per month} = p \cdot m \cdot i \cdot a \cdot b \cdot s \cdot f \quad (1)$$

where: p=average population in the locality; m=average proportion of the population infected; i=proportion of the infected individuals who are infectious; a=average number of mosquitoes per person in the locality, per month; b=proportion of uninfected mosquitoes which feed on man; s=proportion of mosquitoes which survive through the extrinsic incubation period; f=proportion of infectious mosquitoes which feed on man.

This simple equation was a direct precursor of several fertile themes in twentieth century epidemiology.

Ross's mathematical theory went through two major developmental phases. The first was published as a lengthy appendix in the second edition of his book 'The Prevention of Malaria', in 1911(*a*). An abbreviated form of the argument was published by Ross as an article in the same year (1911*b*, *c*). In this work he began to generalize his approach beyond just the malaria situation, and to discuss epidemiological problems in a totally abstract form, calling them 'happenings'. In Ross's (1911*a*) own words:

> 'We shall deal with time-to-time variations not only of malaria, but of all disease, and not only of diseases of man, but those of any living organisms. Still further as infection is only of one of many kinds of events which may happen to such organisms, we shall deal with *happenings* in general.'

Working from a set of simple assumptions, Ross derived a system of equations defining the incidence and prevalence patterns which would be expected for different sorts of happening within a host population. Most of this work was presented in the language of the finite calculus, as finite difference equations. In effect, the method is an extension of the simple equation (1) above. We find equations like the following, which can be iterated in order to calculate the number of infected individuals (z_t, z_t+1) in successive discrete time periods (from t to $t+1$):

$$a_t+1=(1-h)\,v\,a_t+H\,V\,z_t$$
$$z_t+1=h\,v\,a_t+(1-H)V\,z_t \quad (2)$$

where a is the number uninfected; z is the number infected; h is the infection rate; H is the recovery rate; v, V refer to births, deaths, immigrations and emigrations of affected and unaffected individuals.

The third and final development of this 'theory of happenings' appeared in 1916 (*see also* Ross 1915, Ross & Hudson 1917), in the Proceedings of the Royal Society, under the title: 'An application of the theory of probabilities to the study of *a priori* pathometry'. This was the final flowering of Ross's theory, now clothed in the language of the infinitesimal calculus, as a system of differential equations. An example follows:

$$dx/dt = h(1-x) - (N+r)x \qquad (3)$$

where x is the proportion affected among individuals in the population; dx/dt is the rate of change of that proportion with time; N is the birth rate among the affected individuals; h is the infection, or 'happening' rate; and r is the reversion, or recovery rate.

The development of Ross's methodology is clear from these equations: from simple arithmetic product expression; to difference equations; to differential equations.

The Essence of Ross's a priori *Pathometry*

What is, or was, so special about the content of Ross's theory, the theory ultimately known as the *a priori* pathometry? The question is perhaps most easily answered with reference to the scientific background against which Ross produced his work. There was but a meagre tradition of mathematical epidemiology at that time. Most of the small literature drew directly upon a technique for fitting symmetrical curves through epidemic returns data, which had been suggested by William Farr in his second Report as Registrar General, in 1840 (*see also* Farr 1866, Evans 1876, Brownlee 1906, 1915). The important thing is that this previous work was based upon the analysis of sets of actual data, in the form of morbidity or mortality reports. It did not begin, as did Ross's theory of happenings, with assumptions about the mechanism of transmission of the condition in the population. Ross described the different approaches to the analysis of epidemiological phenomena in the following way (Ross 1916, p 205):

'The whole subject is capable of study by two distinct methods which are used in other branches of science, which are complementary of each other, and which should converge towards the same results – the *a posteriori* and the *a priori* methods. In the former we commence with observed statistics, endeavour to fit analytical laws to them, and so work backwards to the underlying cause (as done in much statistical work of the day); and in the latter we assume a knowledge of the causes, construct our differential equations on that supposition, follow up the logical consequences, and finally test the calculated results by comparing them with the observed statistics.'

Needless to say, this latter method, dubbed '*a priori*' by Ross, fairly describes the structure of the logical argument underlying the main use of models by epidemiologists and health statisticians today. It is fully consistent with what is often termed the 'hypothetico-deductive' method, in that deductive mathematical models become tools for the testing of epidemiological hypotheses.

Originality of the Method and Ross's Claim on Priority

Ross (1916) claimed to have been the first to apply this so-called *a priori* method in epidemiological research. From my reading of the literature of that era, I would, in general, concur with his claim. No one before – and few since – had so systematically, and so philosophically adopted this approach to the description of epidemiological phenomena.

On the other hand, like most great ideas in the sciences this one had its precursors, its other proponents who groped in the same direction, yet failed to define and utilize the method so clearly as did Ronald Ross. At least two other authors of the period, William Hamer and John Brownlee, made efforts towards a similar methodology.

Hamer's theoretical work is apparently restricted to a single paper (Hamer 1906). Oddly enough, the paper was never cited by Ross. Hamer's interest was in the periodicity of certain epidemic phenomena, for example, the biennial epidemics of measles. He found that he could generate roughly comparable epidemic curves by a simple algebraic manœuvre based on assumptions of constant 'virulence' and constant introduction of new susceptibles (i.e. newborn children) into the population. His method was crude, but could be fairly described as *a priori*.

John Brownlee's early contribution to the *a priori* method was equally primitive. The majority of his work was of the sort called '*a posteriori*' by Ross – that is, it was based upon the fitting of various mathematical curve forms to epidemic returns data. The shape of such curves, and especially their asymmetry or skewness, was thus of great concern to John Brownlee. In one of his early treatments of this subject, Brownlee (1906) approached the question of the asymmetry of epidemic curves in a novel way:

The striking fact is that epidemics in general hold a course whose constants with very great regularity are those of a single member of the large class of frequency distributions [Pearson's Type IV] . . . The investigation of this is much more easily attempted *a posteriori*. The assumption that the infectivity of an organism is constant, leads to epidemic forms which have no accordance with the actual facts . . . '

There is a paradox in this passage. Brownlee was here implicitly using an *a priori* methodology, in that he speaks of constructing a model (or 'epidemic form') on the basis of assumptions about the mechanism of transmission – yet he calls the method '*a posteriori*', in what is a direct contradiction to the terminology later defined by Ronald Ross. It is interesting that Ross, although he cited this paper by Brownlee several times, never commented either on Brownlee's method, nor on the conflicting terminology used.

Notwithstanding these other publications, Ross can fairly be given the major share of credit for the development of the *a priori* methodology.

Relevance of Ross's Work to Contemporary Epidemiology

Mathematical models of one sort or another are extensively used in epidemiological work today. Many of these models contain assumptions about the mechanism of disease transmission, and are designed to provide expected values for the incidence or prevalence of some disease in a population, which may then be compared with actual observed values. As such, these models are direct descendants of Ross's *a priori* pathometry. In that sense, the fertility of Ross's approach, and its relevance to the science of today, are obvious.

But there are subtler relics of Ross's work in today's literature, which further emphasize the heritage of Ronald Ross. For example, many contemporary students of the epidemiology of infectious disease employ a notation inherited from Ross. Inoculation rates are frequently given the symbol h, regardless of whether the parasite under consideration be plasmodium (Macdonald 1957, Dietz *et al.* 1974), schistosoma (Macdonald 1965), or babesia (Mahoney 1969). This symbol was introduced by Ross (1911*a*), as the pivotal element in his general theory of happenings – h may be an inoculation rate in a particular instance, but it is the *happening* rate in general.

In conclusion, we may return to that first epidemiological model formulated by Ross, and point out some of its recent descendants. We recall that Ross's first description of the transmission cycle of malaria was a simple product expression, defining the number of new malaria infections delivered per month to a population living in an endemic area:

$$\text{Number of new infections} = p\cdot m\cdot i\cdot a\cdot b\cdot s\cdot f \qquad (1)$$

This simple technique of stringing out the several steps in a biological process, in a linear fashion, is in itself a very useful one. Just as Ross began his formulation of malaria in this manner, so initial attempts at the quantifying of filariasis (Beye & Gurian 1960) and schistosomiasis (Hairston 1962) were phrased in this same way.

But Ross's initial equation bears a more impressive relationship to contemporary work than just in notation or general structure. Its specific structure was also a herald of future work.

In considering the condition of endemic, stable malaria, Ross made the logical assumption that the number of new infections, per unit time, should be equivalent to the number of recoveries. In Ross's own notation the number of recoveries per month should be: $r\cdot m\cdot p$, where r is the recovery rate, and $m\cdot p$ equals, as before, the number of persons infected with malaria. Setting this equal to the number of new infections, we have:

$$r = i\cdot a\cdot b\cdot s\cdot f \qquad (4)$$

However, f and b may be considered equal, being but the man-biting habits of noninfectious and infectious mosquitoes, respectively. (This was recognized by Ross.) Thus:

$$r = i\cdot a\cdot b^2\cdot s \qquad (5)$$

This equation can be solved for a, the density of the mosquito population in relation to man:

$$a = \frac{r}{b^2}\cdot\frac{1}{i}\cdot\frac{1}{s} \qquad (6)$$

Defined in this way, a is the 'critical mosquito density', below which malaria cannot be maintained in the human population. This expression (6) turns out to be very similar to one derived by Ross's successor, Professor George Macdonald (1957), half a century later. Macdonald's equation for the critical density of mosquitoes was (here we maintain Ross's notation – *see* Appendix):

$$a = \frac{r}{b^2}\cdot\frac{1}{g}\cdot\frac{(-\mathrm{Log}_e p)}{p^n} \qquad (7)$$

Two differences are evident between equations (6) and (7). The first is in Macdonald's substitution of the g parameter for Ross's i. These parameters are similarly conceived, but apply to different hosts: Macdonald's g is the proportion of infected *mosquitoes* (with sporozoites in their salivary glands) which are actually infectious;

whereas Ross's i refers to the proportion of infected *persons* who are actually infectious (gametocytæmic). Perhaps an ideal model should incorporate both of these parameters.

The second difference between these expressions is in Macdonald's substitution of the $p^n/(-\text{Log}_e p)$ term for Ross's s. Both refer to the same biological factor, the probability and duration of survival of the mosquito after the extrinsic incubation period of n days. Macdonald's more sophisticated handling of this parameter is based on the assumption of a constant daily survival rate (p) of mosquitoes in nature. This was a crucial difference, however, as it allowed Macdonald to investigate the effect of changes in such survival rates, on the transmission of malaria. This was of importance because Macdonald was working in the era of residual insecticides, when man at last had the capacity to manipulate this daily survival rate factor in the field.

Here again we witness evidence of greatness in Ross's idea – evidence of its durability, its strength to last and form a base for the science of future years. We need little wonder that towards the end of his life, Ronald Ross, the man who incriminated the mosquito in the transmission of malaria, would write: 'In my own opinion my principal work has been to establish the general laws of epidemics' (Ross, date uncertain: *see* Beaumont 1974). His work on the *a priori* pathometry was indeed one of the great conceptual advances in the science of epidemiology.

APPENDIX

Expression (7) in this paper is analogous to equation (59) in Macdonald's (1957) text. According to Macdonald's notation:

$$m = \frac{-r \cdot Log_e p}{a^2 \cdot b \cdot p^n}$$

where: m=the anopheline density in relation to man (Ross's a); r=the recovery rate from a single inoculum (*see* Fine 1975); p=probability a mosquito survives through one day; a=the average number of men bitten by one female mosquito in one day (Ross's b); b=the proportion of mosquitoes with sporozoites in their glands which are actually infective; n=time (in days) for completion of the extrinsic cycle. It will be noted that Macdonald's notation is incompatible with that of Ross, as used in this paper.

Ross used expression (6) in order to derive a rough estimate of the minimal mosquito population size which was consistent with the maintenance of malaria in a human population. His numerical estimates for the several parameters were based more on intuition and general experience than on specific experimental results. Taking r, the (monthly) recovery rate in man, as approximately 0.2; b, the man-biting habit of mosquitoes as 0.25; i, the proportion of gametocyte carriers among infected individuals as 0.25; and s the probability of mosquito survival through the extrinsic cycle as 0.33; Ross calculated:

$$a = \frac{0.2}{(0.25)^2\,(0.25)\,(0.33)} \simeq 40$$

This estimate of 40 mosquitoes (per man, per month) was repeatedly cited by Ross as a rough guideline to the threshold size of the mosquito population required for the maintenance of malaria (Ross, 1908, 1910, 1911*a*, 1928, 1929). This was his deductive proof that mere reduction, and not necessarily total eradication, of mosquito population would be sufficient to eliminate malaria.

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